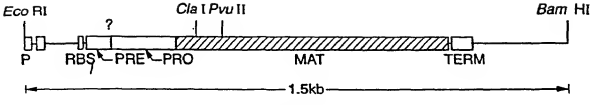

FIG._1A

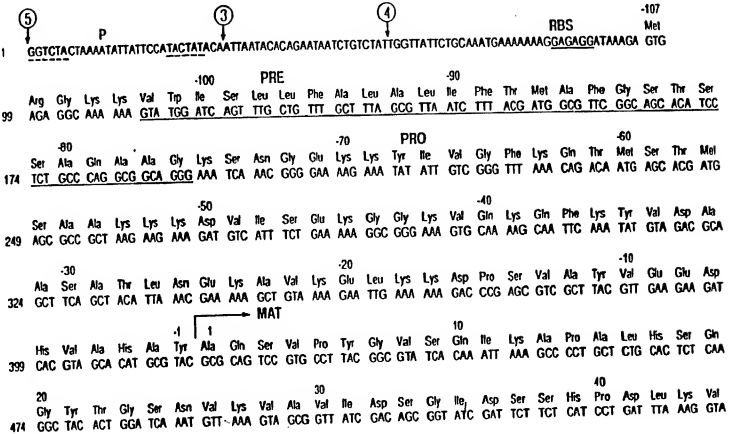
⑤
③
④
P
RBS
-107
Met
1 GGTCTACTAAAATATTATTCCATACTATACAATTAATACACAGAATAATCTGTCTATTGGTTATTCTGCAAATGAAAAAAGGAGAGGATAAAGA GTG
-100
PRE
-90
Arg Gly Lys Lys Val Trp Ile Ser Leu Leu Phe Ala Leu Ala Leu Ile Phe Thr Met Ala Phe Gly Ser Thr Ser
99 AGA GGC AAA AAA GTA TGG ATC AGT TTG CTG TTT GCT TTA GCG TTA ATC TTT ACG ATG GCG TTC GGC AGC ACA TCC
-80
-70
PRO
-60
Ser Ala Gln Ala Ala Gly Lys Ser Asn Gly Glu Lys Lys Tyr Ile Val Gly Phe Lys Gln Thr Met Ser Thr Met
174 TCT GCC CAG GCG GCA GGG AAA TCA AAC GGG GAA AAG AAA TAT ATT GTC GGG TTT AAA CAG ACA ATG AGC ACG ATG
-50
-40
Ser Ala Ala Lys Lys Lys Asp Val Ile Ser Glu Lys Gly Gly Lys Val Gln Lys Gln Phe Lys Tyr Val Asp Ala
249 AGC GCC GCT AAG AAG AAA GAT GTC ATT TCT GAA AAA GGC GGG AAA GTG CAA AAG CAA TTC AAA TAT GTA GAC GCA
-30
-20
-10
Ala Ser Ala Thr Leu Asn Glu Lys Ala Val Lys Glu Leu Lys Lys Asp Pro Ser Val Ala Tyr Val Glu Glu Asp
324 GCT TCA GCT ACA TTA AAC GAA AAA GCT GTA AAA GAA TTG AAA AAA GAC CCG AGC GTC GCT TAC GTT GAA GAA GAT
MAT
-1
1
10
His Val Ala His Ala Tyr Ala Gln Ser Val Pro Tyr Gly Val Ser Gln Ile Lys Ala Pro Ala Leu His Ser Gln
399 CAC GTA GCA CAT GCG TAC GCG CAG TCC GTG CCT TAC GGC GTA TCA CAA ATT AAA GCC CCT GCT CTG CAC TCT CAA
20
30
40
Gly Tyr Thr Gly Ser Asn Val Lys Val Ala Val Ile Asp Ser Gly Ile Asp Ser Ser His Pro Asp Leu Lys Val
474 GGC TAC ACT GGA TCA AAT GTT AAA GTA GCG GTT ATC GAC AGC GGT ATC GAT TCT TCT CAT CCT GAT TTA AAG GTA

FIG._1B - 1

TOE2TO" 08089260

50 Pro Asn 60 Asp
Ala Gly Gly Ala Ser Met Val Pro Ser Glu Thr Asn Pro Phe Gln Asp Asn Asn Ser His Gly Thr His Val Ala
549 GCA GGC GGA GCC AGC ATG GTT CCT TCT GAA ACA AAT CCT TTC CAA GAC AAC AAC TCT CAC GGA ACT CAC GTT GCC

70 80 Ser Ala 90
Gly Thr Val Ala Ala Leu Asn Asn Ser Ile Gly Val Leu Gly Val Ala Pro Ser Ala Ser Leu Tyr Ala Val Lys
624 GGC ACA GTT GCG GCT CTT AAT AAC TCA ATC GGT GTA TTA GGC GTT GCG CCA AGC GCA TCA CTT TAC GCT GTA AAA

Asp Ala 100 110
Val Leu Gly Ala Asp Gly Ser Gly Gln Tyr Ser Trp Ile Ile Asn Gly Ile Glu Trp Ala Ile Ala Asn Asn Met
699 GTT CTC GGT GCT GAC GGT TCC GGC CAA TAC AGC TGG ATC ATT AAC GGA ATC GAG TGG GCG ATC GCA AAC AAT ATG

120 130 140
Asp Val Ile Asn Met Ser Leu Gly Gly Pro Ser Gly Ser Ala Ala Leu Lys Ala Ala Val Asp Lys Ala Val Ala
774 GAC GTT ATT AAC ATG AGC CTC GGC GGA CCT TCT GGT TCT GCT GCT TTA AAA GCG GCA GTT GAT AAA GCC GTT GCA

150 Ser Thr 160
Ser Gly Val Val Val Val Ala Ala Ala Gly Asn Glu Gly Thr Ser Gly Ser Ser Ser Thr Val Gly Tyr Pro Gly
849 TCC GGC GTC GTA GTC GTT GCG GCA GCC GGT AAC GAA GGC ACT TCC GGC AGC TCA AGC ACA GTG GGC TAC CCT GGT

170 180 190
Lys Tyr Pro Ser Val Ile Ala Val Gly Ala Val Asp Ser Ser Asn Gln Arg Ala Ser Phe Ser Ser Val Gly Pro
924 AAA TAC CCT TCT GTC ATT GCA GTA GGC GCT GTT GAC AGC AGC AAC CAA AGA GCA TCT TTC TCA AGC GTA GGA CCT

200 210
Glu Leu Asp Val Met Ala Pro Gly Val Ser Ile Gln Ser Thr Leu Pro Gly Asn Lys Tyr Gly Ala Tyr Asn Gly
999 GAG CTT GAT GTC ATG GCA CCT GGC GTA TCT ATC CAA AGC ACG CTT CCT GGA AAC AAA TAC GGG GCG TAC AAC GGT

220 230 240
Thr Ser Met Ala Ser Pro His Val Ala Gly Ala Ala Ala Leu Ile Leu Ser Lys His Pro Asn Trp Thr Asn Thr
1074 ACG TCA ATG GCA TCT CCG CAC GTT GCC GGA GCG GCT GCT TTG ATT CTT TCT AAG CAC CCG AAC TGG ACA AAC ACT

FIG._1B-2

```
                                    250 Gln                                                 260
     Gln  Val  Arg  Ser  Ser  Leu  Glu  Asn  Thr  Thr  Thr  Lys  Leu  Gly  Asp  Ser  Phe  Tyr  Tyr  Gly  Lys  Gly  Leu  Ile  Asn
1149 CAA  GTC  CGC  AGC  AGT  TTA  GAA  AAC  ACC  ACT  ACA  AAA  CTT  GGT  GAT  TCT  TTC  TAC  TAT  GGA  AAA  GGG  CTG  ATC  AAC

     270                      275
     Val  Gln  Ala  Ala  Ala  Gln  OC                    TERM
1224 GTA  CAG  GCG  GCA  GCT  CAG  TAA  AACATAAAAAACCGGCCTTGGCCCCGCCGGTTTTTTATTTTTCTTCCTCCGCATGTTCAATCCGCTCC

1316 ATAATCGACGGATGGCTCCCTCTGAAAATTTTAACGAGAAACGGCGGGTTGACCCGGCTCAGTCCCGTAACGGCCAAGTCCTGAAACGTCTCAATCGCCG

1416 CTTCCCGGTTTCCGGTCAGCTCAATGCCGTAACGGTCGGCGGCGTTTTCCTGATACCGGGAGACGGCATTCGTAATCGGATC
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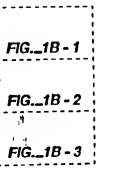
FIG._1B - 3

FIG._1B



CONSERVED RESIDUES IN SUBTILISINS FROM *BACILLUS AMYLOLIQUEFACIENS*

```
1                   10                  20
A Q S V P . G . . . . . A P A . H . . G

21                  30                  40
. T G S . V K V A V . D . G . . . . H P

41                  50                  60
D L . . . G G A S . V P . . . . . Q D

61                  70                  80
. N . H G T H V A G T . A A L N N S I G

81                  90                  100
V L G V A P S A . L Y A V K V L G A . G

101                 110                 120
S G . . S . L . . G . E W A . N . . . .

121                 130                 140
V . N . S L G . P S . S . . . . . A . .

141                 150                 160
. . . . . G V . V V A A . G N . G . . .

161                 170                 180
. . . . . Y P . . Y . . . . A V G A .

181                 190                 200
D . . N . . A S F S . . G . . L D . . A

201                 210                 220
P G V . . Q S T . P G . . Y . . . N G T

221                 230                 240
S M A . P H V A G A A A L . . . K . . .

241                 250                 260
W . . . Q . R . . L . N T . . . L G . .

261                 270
. . Y G . G L . N . . A A . .
```

FIG._2

COMPARISON OF SUBTILISIN SEQUENCES FROM:
B.amyloliquefaciens
B.subtilis
B.licheniformis
B.lentus

```
01                  10                  20                  30
A Q S V P Y G V S Q I K A P A L H S Q G Y T G S N V K V A V I D S G I D S S H P
A Q S V P Y G I S Q I K A P A L H S Q G Y T G S N V K V A V I D S G I D S S H P
A Q T V P Y G I P L I K A D K V Q A Q G F K G A N V K V A V L D T G I Q A S H P
A Q S V P W G I S R V Q A P A A H N R G L T G S G V K V A V L D T G I S T * H P

41                  50                  60                  70
D L K V A G G A S M V P S E T N P F Q D N N S H G T H V A G T V A A L N N S I G
D L N V R G G A S F V P S E T N P Y Q D G S S H G T H V A G T I A A L N N S I G
D L N V V G G A S F V A G E A Y N * T D G N G H G T H V A G T V A A L D N T T G
D L N I R G G A S F V P G E * P S T Q D G N G H G T H V A G T I A A L N N S I G

81                  90                  100                 110
V L G V A P S A S L Y A V K V L G A D G S G Q Y S W I I N G I E W A I A N N M D
V L G V S P S A S L Y A V K V L D S T G S G Q Y S W I I N G I E W A I S N N M D
V L G V A P S V S L Y A V K V L N S S G S G S Y S G I V S G I E W A T T N G M D
V L G V A P S A E L Y A V K V L G A S G S G S V S S I A Q G L E W A G N N G M H

121                 130                 140                 150
V I N M S L G G P S G S A A L K A A V D K A V A S G V V V V A A A G N E G T S G
V I N M S L G G P T G S T A L K T V V D K A V S S G I V V A A A A G N E G S S G
V I N M S L G G A S G S T A M K Q A V D N A Y A R G V V V V A A A G N S G N S G
V A N L S L G S P S P S A T L E Q A V N S A T S R G V L V V A A S G N S G A G S
```

FIG._3A

```
161                 170                   180                   190
S S S T V G Y P G K Y P S V I A V G A V D S S N Q R A S F S S V G P E L D V M A
S T S T V G Y P A K Y P S T I A V G A V N S S N Q R A S F S S A G S E L D V M A
S T N T I G Y P A K Y D S V I A V G A V D S N S N R A S F S S V G A E L E V M A
* * * * I S Y P A R Y A N A M A V G A T D Q N N N R A S F S Q Y G A G L D I V A

201                 210                   220                   230
P G V S I Q S T L P G N K Y G A Y N G T S M A S P H V A G A A A L I L S K H P N
P G V S I Q S T L P G G T Y G A Y N G T S M A T P H V A G A A A L I L S K H P T
P G A G V Y S T Y P T N T Y A T L N G T S M A S P H V A G A A A L I L S K H P N
P G V N V Q S T Y P G S T Y A S L N G T S M A T P H V A G A A A L V K Q K N P S

241                 250                   260                   270
W T N T Q V R S S L E N T T T K L G D S F Y Y G K G L I N V Q A A A Q
W T N A Q V R D R L E S T A T Y L G N S F Y Y G K G L I N V Q A A A Q
L S A S Q V R N R L S S T A T Y L G S S F Y Y G K G L I N V E A A A Q
W S N V Q I R N H L K N T A T S L G S T N L Y G S G L V N A E A A T R
```

FIG._3B

FIG._3

FIG._3A
FIG._3B

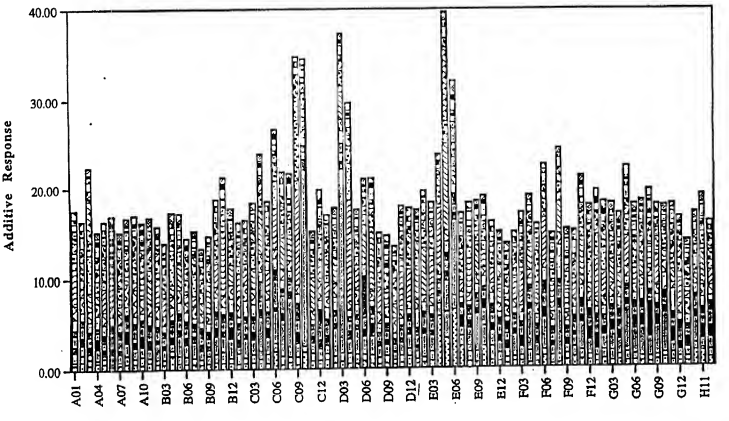


FIG. 4

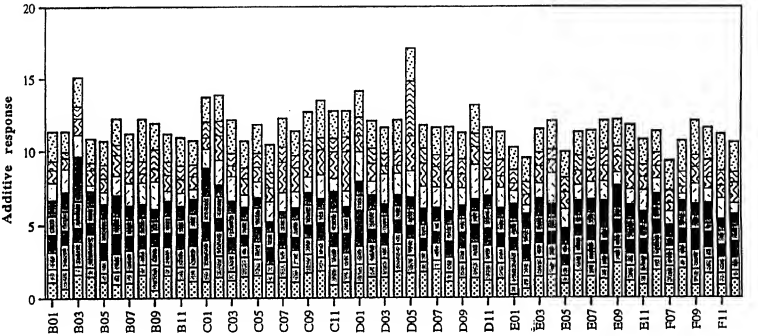


FIG. 5

1	A12	IKDFHVYFRESRDAG
2	A11	LEQAVNSATSRGVLV
3	A10	AQSVPWGISRVQAPA
4	A9	VPWGISRVQAPAAHN
5	A8	GISRVQAPAAHNRGL
6	A7	RVQAPAAHNRGLTGS
7	A6	APAAHNRGLTGSGVK
8	A5	AHNRGLTGSGVKVAV
9	A4	RGLTGSGVKVAVLDT
10	A3	TGSGVKVAVLDTGIS
11	A2	GVKVAVLDTGISTHP
12	A1	VAVLDTGISTHPDLN
13	B12	LDTGISTHPDLNIRG
14	B11	GISTHPDLNIRGGAS
15	B10	THPDLNIRGGASFVP
16	B9	DLNIRGGASFVPGEP
17	B8	IRGGASFVPGEPSTQ
18	B7	GASFVPGEPSTQDGN
19	B6	FVPGEPSTQDGNGHG
20	B5	GEPSTQDGNGHGTHV
21	B4	STQDGNGHGTHVAGT
22	B3	DGNGHGTHVAGTIAA
23	B2	GHGTHVAGTIAALNN
24	B1	THVAGTIAALNNSIG
25	C12	AGTIAALNNSIGVLG
26	C11	IAALNNSIGVLGVAP
27	C10	LNNSIGVLGVAPSAE
28	C9	SIGVLGVAPSAELYA
29	C8	VLGVAPSAELYAVKV
30	C7	VAPSAELYAVKVLGA
31	C6	SAELYAVKVLGASGS
32	C5	LYAVKVLGASGSGSV
33	C4	VKVLGASGSGSVSSI
34	C3	LGASGSGSVSSIAQG
35	C2	SGSGSVSSIAQGLEW
36	C1	GSVSSIAQGLEWAGN
37	D12	SSIAQGLEWAGNNGM
38	D11	AQGLEWAGNNGMHVA
39	D10	LEWAGNNGMHVANLS
40	D9	AGNNGMHVANLSLGS
41	D8	NGMHVANLSLGSPSP
42	D7	HVANLSLGSPSPSAT
43	D6	NLSLGSPSPSATLEQ
44	D5	LGSPSPSATLEQAVN
45	D4	PSPSATLEQAVNSAT
46	D3	SATLEQAVNSATSRG
47	D2	LEQAVNSATSRGVLV
48	D1	AVNSATSRGVLVVAA
49	E12	SATSRGVLVVAASGN
50	E11	SRGVLVVAASGNSGA
51	E10	VLVVAASGNSGAGSI
52	E9	VAASGNSGAGSISYP
53	E8	SGNSGAGSISYPARY
54	E7	SGAGSISYPARYANA
55	E6	GSISYPARYANAMAV
56	E5	SYPARYANAMAVGAT
57	E4	ARYANAMAVGATDQN
58	E3	ANAMAVGATDQNNNR
59	E2	MAVGATDQNNNRASF
60	E1	GATDQNNNRASFSQY
61	F12	DQNNNRASFSQYGAG
62	F11	NNRASFSQYGAGLDI
63	F10	ASFSQYGAGLDIVAP
64	F9	SQYGAGLDIVAPGVN
65	F8	GAGLDIVAPGVNVQS
66	F7	LDIVAPGVNVQSTYP
67	F6	VAPGVNVQSTYPGST
68	F5	GVNVQSTYPGSTYAS
69	F4	VQSTYPGSTYASLNG
70	F3	TYPGSTYASLNGTSM
71	F2	GSTYASLNGTSMATP
72	F1	YASLNGTSMATPHVA
73	G12	LNGTSMATPHVAGAA
74	G11	TSMATPHVAGAAALV
75	G10	ATPHVAGAAALVKQK
76	G9	HVAGAAALVKQKNPS
77	G8	GAAALVKQKNPSWSN
78	G7	ALVKQKNPSWSNVQI
79	G6	KQKNPSWSNVQIRNH
80	G5	NPSWSNVQIRNHLKN
81	G4	WSNVQIRNHLKNTAT
82	G3	VQIRNHLKNTATSLG
83	G2	RNHLKNTATSLGSTN
84	G1	LKNTATSLGSTNLYG
85	H12	TATSLGSTNLYGSGL
86	H11	SLGSTNLYGSGLVNA
87	H10	STNLYGSGLVNAEAA
88	H9	NLYGSGLVNAEAATR

FIG. 6A

1	A12	IKDFHVYFRESRDAG	49	E12	KKIDVLNLSIGGPDF
2	A11	DAELHIFRVFTNNQV	50	E11	DVLNLSIGGPDFMDH
3	A10	PLRRASLSLGSGFWH	51	E10	NLSIGGPDFMDHPFV
4	A9	RASLSLGSGFWHATG	52	E9	IGGPDFMDHPFVDKV
5	A8	LSLGSGFWHATGRHS	53	E8	PDFMDHPFVDKVWEL
6	A7	GSGFWHATGRHSSRR	54	E7	MDHPFVDKVWELTAN
7	A6	FWHATGRHSSRRLLR	55	E6	PFVDKVWELTANNVI
8	A5	ATGRHSSRRLLRAIP	56	E5	DKVWELTANNVIMVS
9	A4	RHSSRRLLRAIPRQV	57	E4	WELTANNVIMVSAIG
10	A3	SRRLLRAIPRQVAQT	58	E3	TANNVIMVSAIGNDG
11	A2	LLRAIPRQVAQTLQA	59	E2	NVIMVSAIGNDGPLY
12	A1	AIPRQVAQTLQADVL	60	E1	MVSAIGNDGPLYGTL
13	B12	RQVAQTLQADVLWQM	61	F12	AIGNDGPLYGTLNNP
14	B11	AQTLQADVLWQMGYT	62	F11	NDGPLYGTLNNPADQ
15	B10	LQADVLWQMGYTGAN	63	F10	PLYGTLNNPADQMDV
16	B9	DVLWQMGYTGANVRV	64	F9	GTLNNPADQMDVIGV
17	B8	WQMGYTGANVRVAVF	65	F8	NNPADQMDVIGVGGI
18	B7	GYTGANVRVAVFDTG	66	F7	ADQMDVIGVGGIDFE
19	B6	GANVRVAVFDTGLSE	67	F6	MDVIGVGGIDFEDNI
20	B5	VRVAVFDTGLSEKHP	68	F5	IGVGGIDFEDNIARF
21	B4	AVFDTGLSEKHPHFK	69	F4	GGIDFEDNIARFSSR
22	B3	DTGLSEKHPHFKNVK	70	F3	DFEDNIARFSSRGMT
23	B2	LSEKHPHFKNVKERT	71	F2	DNIARFSSRGMTTWE
24	B1	KHPHFKNVKERTNWT	72	F1	ARFSSRGMTTWELPG
25	C12	HFKNVKERTNWTNER	73	G12	SSRGMTTWELPGGYG
26	C11	NVKERTNWTNERTLD	74	G11	GMTTWELPGGYGRMK
27	C10	ERTNWTNERTLDDGL	75	G10	TWELPGGYGRMKPDI
28	C9	NWTNERTLDDGLGHG	76	G9	LPGGYGRMKPDIVTY
29	C8	NERTLDDGLGHGTFV	77	G8	GYGRMKPDIVTYGAG
30	C7	TLDDGLGHGTFVAGV	78	G7	RMKPDIVTYGAGVRG
31	C6	DGLGHGTFVAGVIAS	79	G6	PDIVTYGAGVRGSGV
32	C5	GHGTFVAGVIASMRE	80	G5	VTYGAGVRGSGVKGG
33	C4	TFVAGVIASMRECQG	81	G4	GAGVRGSGVKGGCRA
34	C3	AGVIASMRECQGFAP	82	G3	VRGSGVKGGCRALSG
35	C2	IASMRECQGFAPDAE	83	G2	SGVKGGCRALSGTSV
36	C1	MRECQGFAPDAELHI	84	G1	KGGCRALSGTSVASP
37	D12	CQGFAPDAELHIFRV	85	H12	CRALSGTSVASPVVA
38	D11	FAPDAELHIFRVFTN	86	H11	LSGTSVASPVVAGAV
39	D10	DAELHIFRVFTNNQV	87	H10	TSVASPVVAGAVTLL
40	D9	LHIFRVFTNNQVSYT	88	H9	ASPVVAGAVTLLVST
41	D8	FRVFTNNQVSYTSWF	89	H8	VVAGAVTLLVSTVQK
42	D7	FTNNQVSYTSWFLDA	90	H7	GAVTLLVSTVQKREL
43	D6	NQVSYTSWFLDAFNY	91	H6	TLLVSTVQKRELVNP
44	D5	SYTSWFLDAFNYAIL	92	H5	VSTVQKRELVNPASM
45	D4	SWFLDAFNYAILKKI	93	H4	VQKRELVNPASMKQA
46	D3	LDAFNYAILKKIDVL	94	H3	RELVNPASMKQALIA
47	D2	FNYAILKKIDVLNLS	95	H2	VNPASMKQALIASAR
48	D1	AILKKIDVLNLSIGG	96	H1	ASMKQALIASARRLP

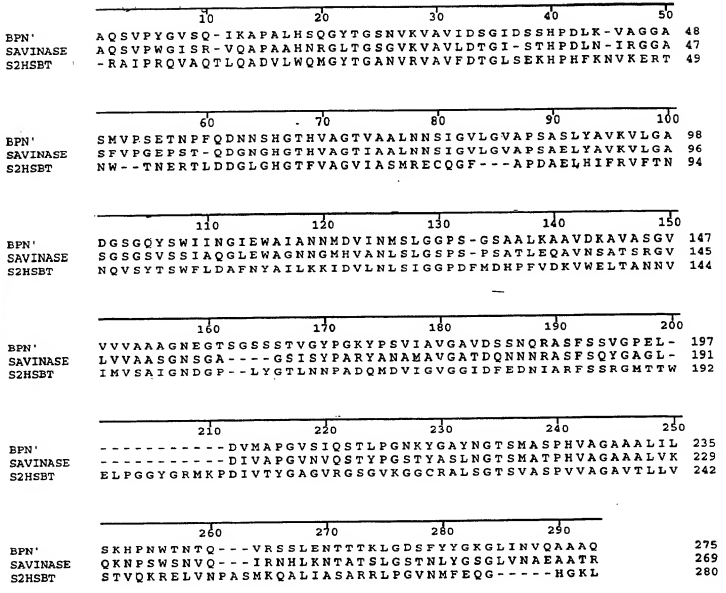
FIG. 6B

97	I12	IKDFHVYFRESRDAG
98	I11	DAELHIFRVFTNNQV
99	I10	KQALIASARRLPGVN
100	I9	LIASARRLPGVNMFE
101	I8	SARRLPGVNMFEQGH
102	I7	RLPGVNMFEQGHGKL
103	I6	GVNMFEQGHGKLDLL
104	I5	MFEQGHGKLDLLRAY
105	I4	QGHGKLDLLRAYQIL
106	I3	GKLDLLRAYQILNSY
107	I2	DLLRAYQILNSYKPQ
108	I1	RAYQILNSYKPQASL
109	J12	QILNSYKPQASLSPS
110	J11	NSYKPQASLSPSYID
111	J10	KPQASLSPSYIDLTE
112	J9	ASLSPSYIDLTECPY
113	J8	SPSYIDLTECPYMWP
114	J7	YIDLTECPYMWPYCS
115	J6	LTECPYMWPYCSQPI
116	J5	CPYMWPYCSQPIYYG

FIG. 6C

MKLVNIWLLLLVVLLCGKKHLGDRLEKKSFEKAPCPGCSHLTLKVEFSSTVVEYEYIVAFNGYFT
AKARNSFISSALKSSEVDNWRIIPRNNPSSDYPSDFEVIQIKEKQKAGLLTLEDHPNIKRVTPQR
KVFRSLKYAESDPTVPCNETRWSQKWQSSRPLRRASLSLGSGFWHATGRHSSRRLLRAIPRQVAQ
TLQADVLWQMGYTGANVRVAVFDTGLSEKHPHFKNVKERTNWTNERTLDDGLGHGTFVAGVIASM
RECQGFAPDAELHIFRVFTNNQVSYTSWFLDAFNYAILKKIDVLNLSIGGPDFMDHPFVDKVWEL
TANNVIMVSAIGNDGPLYGTLNNPADQMDVIGVGGIDFEDNIARFSSRGMTTWELPGGYGRMKPD
IVTYGAGVRGSGVKGGCRALSGTSVASPVVAGAVTLLVSTVQKRELVNPASMKQALIASARRLPG
VNMFEQGHGKLDLLRAYQILNSYKPQASLSPSYIDLTECPYMWPYCSQPIYYGGMPTVVNVTILN
GMGVTGRIVDKPDWQPYLPQNGDNIEVAFSYSSVLWPWSGYLAISISVTKKAASWEGIAQGHVMI
TVASPAETESKNGAEQTSTVKLPIKVKIIPTPPRSKRVLWDQYHNLRYPPGYFPRDNLRMKNDPL
DWNGDHIHTNFRDMYQHLRSMGYFVEVLGAPFTCFDASQYGTLLMVDSEEEYFPEEIAKLRRDVD
NGLSLVIFSDWYNTSVMRKVKFYDENTRQWWMPDTGGANIPALNELLSVWNMGFSDGLYEGEFTL
ANHDMYYASGCSIAKFPEDGVVITQTFKDQGLEVLKQETAVVENVPILGLYQIPAEGGGRIVLYG
DSNCLDDSHRQKDCFWLLDALLQYTSYGVTPPSLSHSGNRQRPPSGAGSVTPERMEGNHLHRYSK
VLEAHLGDPKPRPLPACPRLSWAKPQPLNETAPSNLWKHQKLLSIDLDKVVLPNFRSNRPQVRPL
SPGESGAWDIPGGIMPGRYNQEVGQTIPVFAFLGAMVVLAFFVVQINKAKSRPKRRKPRVKRPQL
MQQVHPPKTPSV

FIG. 7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BPN' AQSVPYGVSQ-IKAPALHSQGYTGSNVKVAVIDSGIDSSHPDLK-VAGGA 48
SAVINASE AQSVPWGISR-VQAPAAHNRGLTGSGVKVAVLDTGI-STHPDLN-IRGGA 47
S2HSBT -RAIPRQVAQTLQADVLWQMGYTGANVRVAVFDTGLSEKHPHFKNVKERT 49
60 70 80 90 100
BPN' SMVPSETNPFQDNNSHGTHVAGTVAALNNSIGVLGVAPSASLYAVKVLGA 98
SAVINASE SFVPGEPST-QDGNGHGTHVAGTIAALNNSIGVLGVAPSAELYAVKVLGA 96
S2HSBT NW--TNERTLDDGLGHGTFVAGVIASMRECQGF---APDAELHIFRVFTN 94
110 120 130 140 150
BPN' DGSGQYSWIINGIEWAIANNMDVINMSLGGPS-GSAALKAAVDKAVASGV 147
SAVINASE SGSGSVSSIAQGLEWAGNNGMHVANLSLGSPS-PSATLEQAVNSATSRGV 145
S2HSBT NQVSYTSWFLDAFNYAILKKIDVLNLSIGGPDFMDHPFVDKVWELTANNV 144
160 170 180 190 200
BPN' VVVAAAGNEGTSGSSSTVGYPGKYPSVIAVGAVDSSNQRASFSSVGPEL- 197
SAVINASE LVVAASGNSGA----GSISYPARYANAMAVGATDQNNNRASFSQYGAGL- 191
S2HSBT IMVSAIGNDGP--LYGTLNNPADQMDVIGVGGIDFEDNIARFSSRGMTTW 192
210 220 230 240 250
BPN' ----------DVMAPGVSIQSTLPGNKYGAYNGTSMASPHVAGAAALIL 235
SAVINASE ----------DIVAPGVNVQSTYPGSTYASLNGTSMATPHVAGAAALVK 229
S2HSBT ELPGGYGRMKPDIVTYGAGVRGSGVKGGCRALSGTSVASPVVAGAVTLLV 242
260 270 280 290
BPN' SKHPNWTNTQ---VRSSLENTTTKLGDSFYYGKGLINVQAAAQ 275
SAVINASE QKNPSWSNVQ---IRNHLKNTATSLGSTNLYGSGLVNAEAATR 269
S2HSBT STVQKRELVNPASMKQALIASARRLPGVNMFEQG-----HGKL 280

FIG. 8

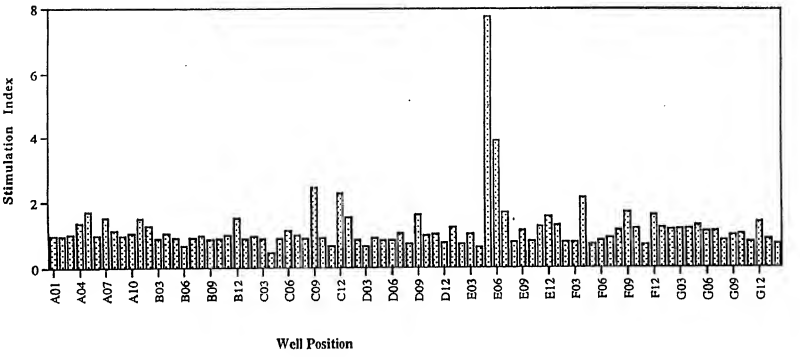


FIG. 9

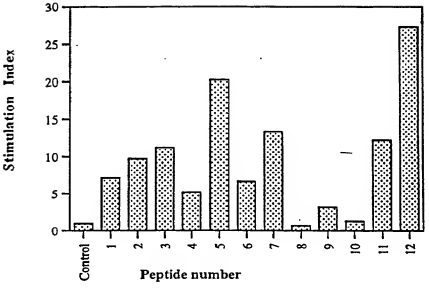
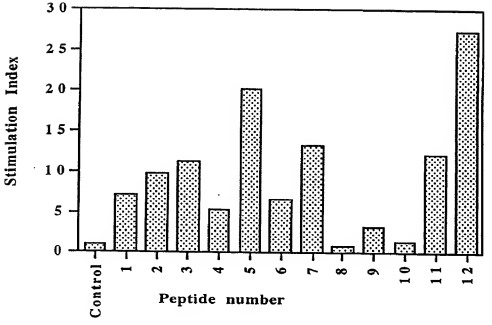


FIG. 10



Peptide number	Sequence
1 (unmodified sequence)	GSISYPARYANAMAV
2	ASISYPARYANAMAV
3	GAISYPARYANAMAV
4	GSASYPARYANAMAV
5	GSIAYPARYANAMAV
6	GSISAPARYANAMAV
7	GSISYAARYANAMAV
8	GSISYPAAYANAMAV
9	GSISYPARAANAMAV
10	GSISYPARYAAAMAV
11	GSISYPARYANAAAV
12	GSISYPARYANAMAA

FIG. 11

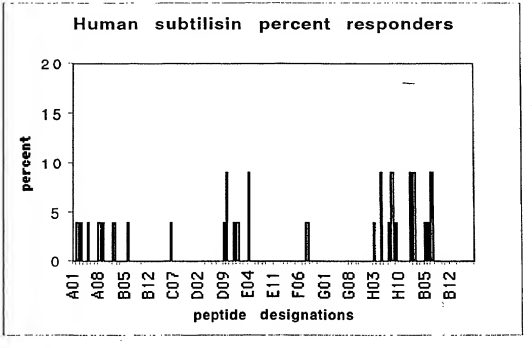

Human subtilisin percent responders
20
15
10
5
0
percent
A01
A08
B05
B12
C07
D02
D09
E04
E11
F06
G01
G08
H03
H10
B05
B12
peptide designations

FIG. 12

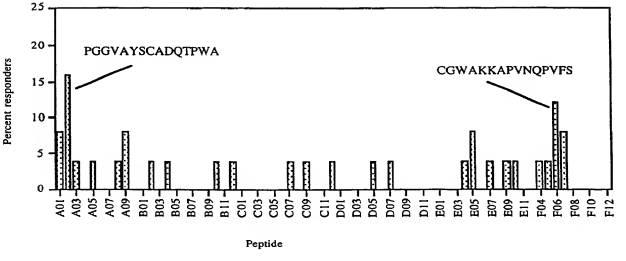

PGGVAYSCADQTPWA
CGWAKKAPVNQPVFS
Percent responders
Peptide
25
20
15
10
5
0
A01
A03
A05
A07
A09
B01
B03
B05
B07
B09
B11
C01
C03
C05
C07
C09
C11
D01
D03
D05
D07
D09
D11
E01
E03
E05
E07
E09
E11
F04
F06
F08
F10
F12

FIG. 13A

```
          1          2          3          4          5
1234567890 1234567890 1234567890 1234567890 1234567890
MRSSPLLPSA VVAALPVLAL AADGRSTRYW DCCKPSCGWA KKAPVNQPVF
SCNANFQRIT DFDAKSGCEP GGVAYSCADQ TPWAVNDDFA LGFAATSIAG
SNEAGWCCAC YELTFTSGPV AGKKMVVQST STGGDLGSNH FDLNIPGGGV
GIFDGCTPQF GGLPGQRYGG ISSRNECDRF PDALKPGCYW RFDWFKNADN
PSFSFRQVQC PAELVARTGC RRNDDGNFFA VQIPSSSTSS PVNQPTSTST
TSTSTTSSPP VQPTTPSGCT AERWAQ
```

FIG. 13B

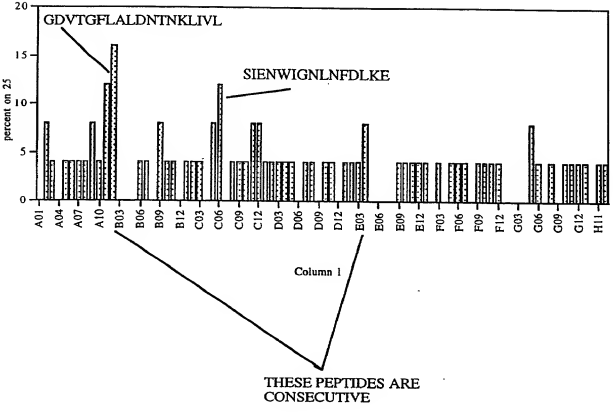

GDVTGFLALDNTNKLIVL
SIENWIGNLNFDLKE
percent on 25
20
15
10
5
0
A01
A04
A07
A10
B03
B06
B09
B12
C03
C06
C09
C12
D03
D06
D09
D12
E03
E06
E09
E12
F03
F06
F09
F12
G03
G06
G09
G12
H11
Column 1
THESE PEPTIDES ARE CONSECUTIVE

FIG. 14A

```
  1 mrsslvlffv sawtalaspi rrevsqdlfn qfnlfaqysa aaȳcgknnda
 51 pagtnitctg nacpevekad atflysfeds gvgdvtgfla ldntnklivl
101 sfrgsrsien wiqnlnfdlk eindicsgcr ghdgftsswr svadtlrqkv
151 edavrehpdy rvvftghslg galatvagad lrgngydidv fsygaprvgn
201 rafaefltvq tggtlyrith tndivprlpp refgyshssp eywiksgtlv
251 pvtrndivki egidatggnn qpnipdipah lwyfgligtc l
```

FIG. 14B

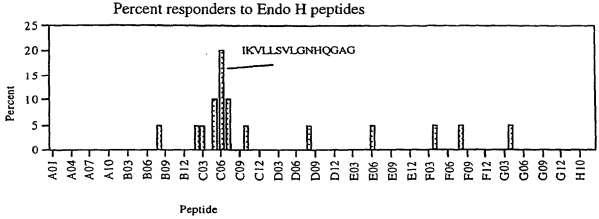


FIG. 15A

```
  1 mftpvrrrvr taalalsaaa alvlgstaas gasatpspap apapapvkqg
 51 ptsvayvevn nnsmlnvgky tladgggnaf dvavifaani nydtgtktay
101 lhfnenvqrv ldnavtqirp lqqqgikvll svlqnhqqag fanfpsqqaa
151 safakqlsda vakygldgvd fddeyaeygn ngtaqpndss fvhlvtalra
201 nmpdkiisly nigpaasrls yggvdvsdkf dyawnpyygt wqvpgialpk
251 aqlspaavei grtsrstvad larrtvdegy gvyltynldg gdrtadvsaf
301 trelygseav rtp
```

FIG. 15B

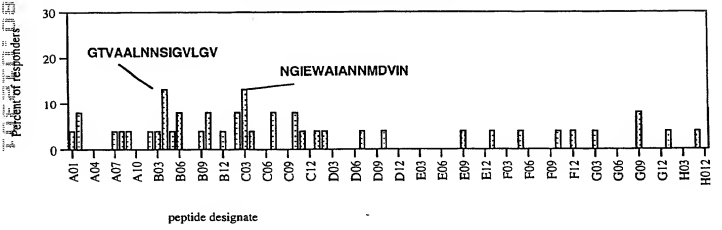

BPN compiled for 22 individuals.
Percent of responders
30
20
10
0
GTVAALNNSIGVLGV
NGIEWAIANNMDVIN
A01
A04
A07
A10
B03
B06
B09
B12
C03
C06
C09
C12
D03
D06
D09
D12
E03
E06
E09
E12
F03
F06
F09
F12
G03
G06
G09
G12
H03
H012
peptide designate

FIG. 16

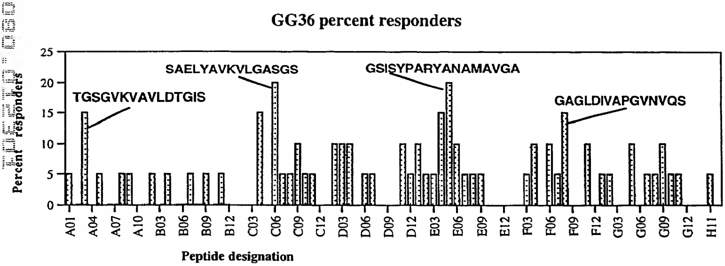

GG36 percent responders
Percent responders
Peptide designation
TGSGVKVAVLDTGIS
SAELYAVKVLGASGS
GSISYPARYANAMAVGA
GAGLDIVAPGVNVQS
0
5
10
15
20
25
A01
A04
A07
A10
B03
B06
B09
B12
C03
C06
C09
C12
D03
D06
D09
D12
E03
E06
E09
E12
F03
F06
F09
F12
G03
G06
G09
G12
H11

FIG. 17

Hybrid enzyme sequence (GG36-BPN)

GG36

AQSVPWGISRVQAPAAHNRGLTGSGVKVAVLDTGISTHPDLNIRGGASFVPGEPSTQDGNGH

BPN

GTHVAGTIAALNNSIGVLGVAPSAELYAVKVLGASGSGSVSSIAQGLEWAGNNGMHVINMSLGGS

Δ

GSAALKAAVDKAVASGVVVVAAAGNEGTSGSSSTVGYPGKYPSVIAVGAVDSSNQRASFSSVGP

ELDVMAPGVSIQSTLPGNKYGAYNGTSMASPHVAGAAALILSKHPNWTNTQVRSSLENTTTKLGD

SFYY GKGLINVQAAAQ

FIG. 18

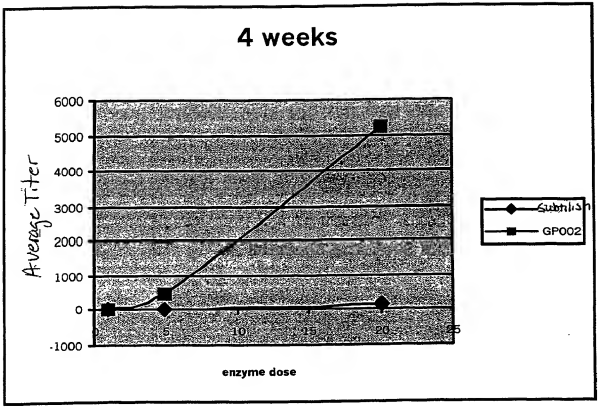

4 weeks
Average Titer
6000
5000
4000
3000
2000
1000
0
-1000
0
5
10
15
20
25
enzyme dose
GP002

FIGURE 19A

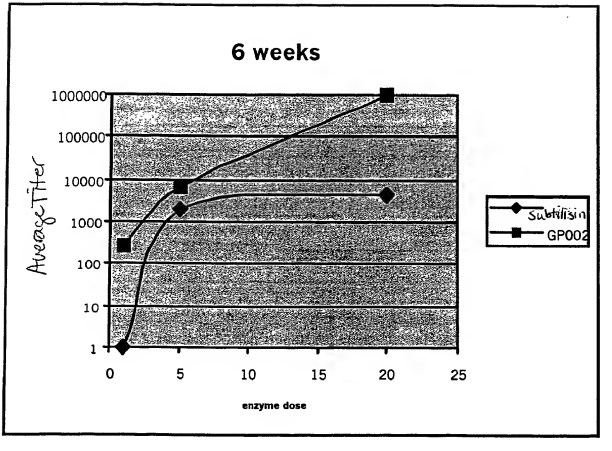

6 weeks
1000000
100000
10000
1000
100
10
1
Average Titer
0
5
10
15
20
25
enzyme dose
Subtilisin
GP002

FIGURE 19B

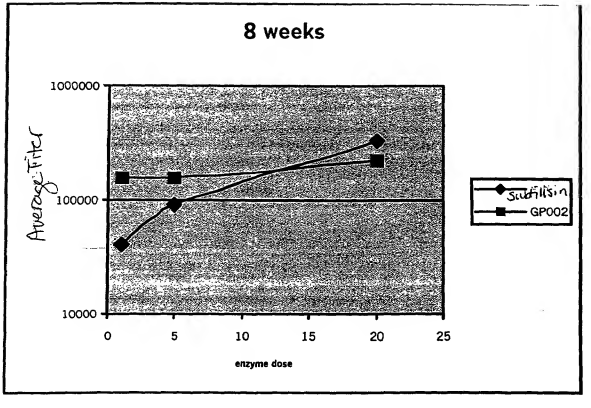


FIGURE 19C

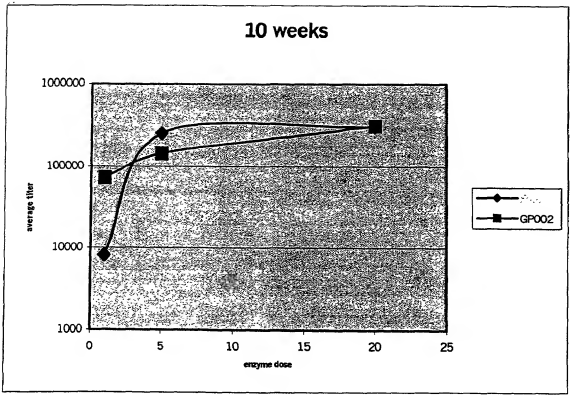

10 weeks
1000000
100000
10000
1000
average titer
0
5
10
15
20
25
enzyme dose
GP002

FIGURE 19D

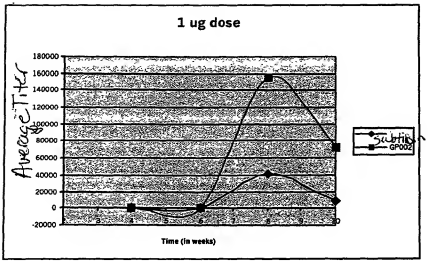


FIGURE 20A

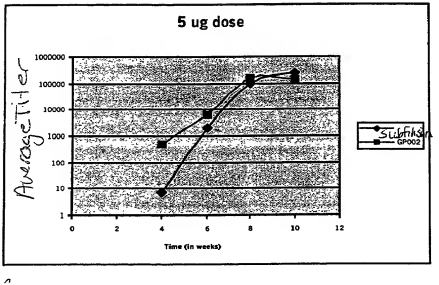

5 ug dose
Average Titer
1000000
100000
10000
1000
100
10
1
0
2
4
6
8
10
12
Time (in weeks)
Stuffish
GP002

FIGURE 20B

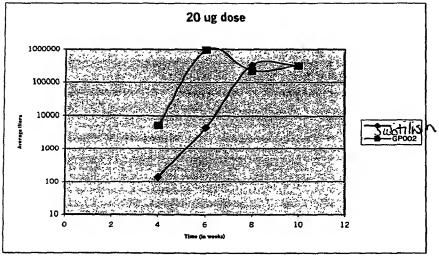


FIGURE 20C

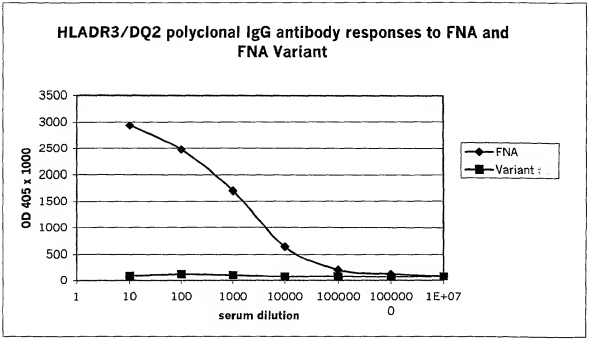

HLADR3/DQ2 polyclonal IgG antibody responses to FNA and FNA Variant
OD 405 x 1000
3500
3000
2500
2000
1500
1000
500
0
1
10
100
1000
10000
100000
1000000
1E+07
serum dilution
FNA
Variant

FIGURE 21